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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1632	6

DATE MAILED: 06/29/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

FILE COPY

Office Action Summary	Application No. 09/446,317	Applicant(s) Wagner et al
	Examiner Richard Schniz r	Group Art Unit 1632

☒ Responsive to communication(s) filed on *Apr 17, 2000*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *35-68* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *35-68* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

A preliminary amendment was received and entered as Paper No. 5 on 4/17/00. Claims 1-34 have been canceled. Claims 35-68 have been added, and are under consideration in this Office Action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 53-57 and 65-68 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention and breadth of the claims. Claims 53-57 are drawn to a composition comprising a therapeutically active nucleic acid. Claims 65-68 are drawn to a pharmaceutical composition comprising a nucleic acid. For the purpose of examination under, or a pharmaceutically 35 U.S.C. 112, first paragraph, "pharmaceutical compositions" must be enabled for therapeutic use. Thus claims 53-57, and 65-68 are drawn to gene therapy, particularly in light of the specification at page 1, lines 21-24; and page 4, lines 23-26.

State of the prior art. At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by two recently published reviews. Verma et al (1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (1998) states that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concludes, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30).

Guidance and working examples in the specification. The invention addresses the issue of gene delivery. However no evidence is presented which would convey to a skilled artisan that the art-recognized problems associated with either gene delivery or gene expression have been solved, and the issue of expression after delivery does not appear to have been addressed.

Predictability of the art. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). In the case of gene therapy in general, the art-accepted problems associated with gene delivery and expression result in a very low predictability of success.

Amount of experimentation. Due to the lack of guidance and working examples in the specification, a skilled artisan would have to perform extensive experimentation in order to develop successful gene therapy protocols utilizing the claimed compositions.

Because gene therapy cannot be practiced with routine success by those of skill in the art, and due to the level of unpredictability of the art, and the lack of examples and guidance in the specification, a skilled artisan would have to perform undue experimentation in order to perform gene therapy with the claimed compositions.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 46-48, and 58-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 46-48 are indefinite. These claims recite complexes with a range of specific molar ratios of polymer to PEI, whereas the specification recites processes for making complexes in which the starting materials are present in amounts within these specified ranges. It is not clear that the reaction mixes disclosed in the specification give rise to the complexes recited in the claims.

Claims 58-63 are indefinite because claim 58 recites "the dilute solutions" without antecedent basis.

Claims 61 and 62 are indefinite because they recite "the physiological value" without antecedent basis. What physiologies are encompassed? Furthermore, these claims refer to "a salt

concentration", but do not define which salt is in consideration. Is it NaCl, KCl, or some combination of salts?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 35-43 and 49 are rejected under 35 U.S.C. 102(e) as being anticipated by either one of Yin et al (US Patent 5,919,442, effective filing date 8/11/95) or Tomalia et al (US Patent 5,714,166, filed 3/7/95).

Yin teaches complexes comprising a nucleic acid and PEI, wherein PEI is covalently modified with a hydrophilic polymer. See Abstract; column 5, lines 46-48; column 12, lines 27-37; column 20, lines 20-57, especially lines 47-50; paragraph bridging columns 27 and 28; column 48, claim 8; and column 49, claim 12. A variety of phosphate to nitrogen ratios are encompassed. See column 29, lines 12-19. The molecular weight of PEI may be from 10,000 to 100,000,000. See column 7, lines 32-41. The hydrophilic polymer may be polyethylene glycol, polyvinylpyrollidone, polyacrylamide, or combinations thereof. See column 5 lines 44-50; and

claim 12, column 48. The complexes may comprise a targeting ligand attached to PEI. See column 18, lines 41-43; column 54, claim 41; and column 57, claim 63.

Thus Yin anticipates the claims.

Tomalia teaches complexes comprising a nucleic acid and PEI, wherein PEI is covalently modified with a hydrophilic polymer. See Abstract; column 4, lines 25-32; paragraph bridging columns 13 and 14; column 22, lines 36-40; and column 48, lines 16-25. A variety of phosphate to nitrogen ratios are encompassed. The molecular weight of PEI may be about 2000 D. See column 70, lines 30-34. The hydrophilic polymer may be polyethylene glycol. The complexes may comprise a targeting ligand attached to PEI. See column 22, lines 15-26, paragraph bridging columns 22 and 23, especially column 23, lines 5-10.

Thus Tomalia anticipates the claims.

Claims 35, 41-45, 49, and 52 are rejected under 35 U.S.C. 102(e) as being anticipated by Bogdanov et al (US Patent 5,871,710, effective filing date of 6/17/94).

Bogdanov teaches a drug delivery composition comprising PEI to which PEG has been covalently attached as a protectant. Polynucleotides may be present as a block copolymer with PEG. See column 5, lines 10-16, and 59-66. The composition may also comprise a targeting group bound to either PEI or PEG. See column 6, lines 36-40. PEG may be present in a molecular weight from 500-10,000 D. See column 15, lines 47-50.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 44-51, and 58-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yin et al (US Patent 5,919,442, effective filing date 8/11/95) or Tomalia et al (US Patent 5,714,166, filed 3/7/95), either one in view of Szoka (US Patent 5,661,025, filed 6/7/95).

Yin teaches complexes comprising a nucleic acid and PEI, wherein PEI is covalently modified with a hydrophilic polymer. See Abstract; column 5, lines 46-48; column 12, lines 27-37; column 20, lines 20-57, especially lines 47-50; paragraph bridging columns 27 and 28; column 48, claim 8; and column 49, claim 12. A variety of phosphate to nitrogen ratios are encompassed. See column 29, lines 12-19. The molecular weight of PEI may be from 10,000 to 100,000,000. See column 7, lines 32-41. The hydrophilic polymer may be polyethylene glycol, polyvinylpyrollidone, polyacrylamide, or combinations thereof. See column 5 lines 44-50; and claim 12, column 48. The complexes may comprise a targeting ligand attached to PEI. The targeting ligand may be a protein, and more specifically a hormone. See column 18, lines 41-43; column 54, claim 41; and column 57, claim 63. DNA may be added to PEI in a solution of water

comprising 50 μg DNA/ml. See column 29, lines 39-41. The solution may be diluted for later use. See column 29, lines 35-39.

Yin is silent with respect to the molecular weight of the hydrophilic polymer, the ratio of hydrophilic polymer to PEI primary amine groups, and the order in which the DNA and the hydrophilic polymer are added to PEI. Yin does not teach transferrin or EGF as targeting ligands.

Tomalia teaches complexes comprising a nucleic acid and PEI, wherein PEI is covalently modified with a hydrophilic polymer. See Abstract; column 4, lines 25-32; paragraph bridging columns 13 and 14; column 22, lines 36-40; and column 48, lines 16-25. A variety of phosphate to nitrogen ratios are encompassed. The molecular weight of PEI may be about 2000 D. See column 70, lines 30-34. The hydrophilic polymer may be polyethylene glycol. The complexes may comprise a targeting ligand attached to PEI. The targeting ligand may be a protein. See column 22, lines 15-26, paragraph bridging columns 22 and 23, especially column 23, lines 5-10. DNA may be added to PEI in a solution of water comprising 50 μg DNA/ml, and then diluted to a concentration of 1-10 μg DNA/ml. See column 49, lines 37-42.

Tomalia is silent with respect to the molecular weight of the hydrophilic polymer, the ratio of hydrophilic polymer to PEI primary amine groups, and the order in which the DNA and the hydrophilic polymer are added to PEI. Tomalia does not teach transferrin or EGF as targeting ligands.

Szoka teaches a self-assembling polynucleotide delivery system comprising dendrimer polycations. The dendrimers are composed of cationic polyamines similar to polyethylenimine.

See column 10, lines 36-46. The complexes may comprise a DNA masking agent, such as PEG, covalently linked to the dendrimer. The PEG may have a molecular weight from 700-20,000 D, and may be present in a ratio of moles of polymer:PEI primary amino groups from 1:3 to 1:33. See column 12, lines 18-43. Szoka also encourages the use of EGF as a targeting ligand, and discloses that transferrin is well known in the art as a targeting ligand. See column 2, lines 43-45; column 3, lines 40-44; and column 14, lines 8-11.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use PEG in the inventions of either Yin or Tomalia in the molecular weights and ratios taught by Szoka. Yin and Tomalia are silent on the molecular weights and ratios of PEG to use in their compositions, but one of ordinary skill in the art would be aware of the teachings of Szoka, and would be motivated to use these molecular weights and ratios of PEG as a starting point in optimization of the complexes because the compositions of Szoka are very similar in structure and function to those of Yin and Tomalia. For example, the compositions all comprise cationic polyamines with primary amino groups involved in a charge interaction with a nucleic acid and a hydrophilic polymer at the periphery of the polymer, and the intended use of the compositions is the delivery of nucleic acids to cells.

It would have been obvious to one of ordinary skill in the art at the time of the invention to prepare the PEI/DNA/PEG complexes of Yin and Tomalia by first mixing the DNA and PEI, and then adding the PEG. One would have been motivated to take this approach because Szoka teaches that PEG is useful as a masking agent which shields DNA from degradation. As such, it

would be obvious to add it to the complex after addition of DNA, thereby maximizing the likelihood that the DNA would be masked. It would have been similarly obvious to use DNA concentrations of about 5-50 or 10-40 μg/ml at a salt concentration below the physiological value in this process because Yin and Tomalia both teach the use of DNA at a concentration of 50 μg/ml in water for the formation of complexes. The use of deionized water is standard operating procedure in molecular biology laboratories, as is well known by one of ordinary skill in the art. Further optimization of the concentration of the complexes for the purpose of transfection is well within the ability of one of ordinary skill in the art, and could reasonably be expected to lead to compositions with the characteristics of claims 63 and 64, particularly in view of the suggestion by Tomalia to dilute the complexes to 1-10 μg DNA/ml (see column 49, lines 37-43).

Thus the invention as a whole was *prima facie* obvious.

Claim 52 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yin or Tomalia et al, either one in view of Szoka, as applied to claims 44-51, and 58-64 above, and further in view of Bogdanov et al (US Patent 5,871,710, effective filing date of 6/17/94).

The teachings of Szoka and either of Yin or Tomalia can be combined to disclose a complex comprising PEI, DNA, a hydrophilic polymer covalently bound to PEI, and a targeting ligand bound to PEI. These references do not teach a targeting ligand bound to the hydrophilic polymer which is bound to PEI.

Bogdanov teaches a drug delivery composition comprising PEI to which PEG has been covalently attached as a protectant. See column 5, lines 10-16, and 59-60. The composition may also comprise a targeting group bound to either PEI or PEG. See column 6, lines 36-40.

It would have been obvious to one of ordinary skill in the art to attach the targeting ligand of Szoka and either Yin or Tomalia to the hydrophilic polymer rather than to PEI, because Bogdanov suggests doing so. One would have been motivated to do this in order to expose the targeting ligand and to thereby ensure that the targeting ligand is not sterically shielded from the target.

Thus the invention as a whole was *prima facie* obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached on Mondays and Thursdays between the hours of 6:20 AM and 3:50 PM, and on Tuesdays, Wednesdays and Fridays between the hours of 7:00 AM and 4:30 PM (Eastern time). The examiner is off every other Friday, but is usually in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached at 703-308-2035. The FAX phone numbers for art unit 1632 are 703-308-4242 and 703-305-3014.

Inquiries of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER

Richard Schnizer, Ph. D.